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LETTERS

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Incidence of vasculitis in rheumatoid arthritis: comment on the article by Turesson et al

To the Editor:

We read with interest the report by Turesson et al on the incidence of vasculitis and other extraarticular manifestations in rheumatoid arthritis (RA) (1). In the long-term study of a community-based cohort of patients with RA, no evidence was found for a decrease in the incidence of severe vasculitis.

As the authors pointed out, their results differ from those reported by Watts et al, who observed a >3-fold decreased incidence of systemic rheumatoid vasculitis from 1988 to 2002 in Norwich, UK (2). Another study, which may have not been mentioned in the report by Turesson et al due to space limitations, evaluated the incidence of severe extraarticular rheumatoid manifestations by reporting the rates of hospitalization in the US (according to the National Institute of Arthritis and Musculoskeletal and Skin Diseases/National Institutes of Health) (3). Again, the rate of hospitalization due to systemic vasculitis decreased by one-third from 1983 to 2001.

Turesson et al give some potential explanation for the discrepancies with the previous results. We would like to suggest another possibility. Although it was extensive, the analysis performed by Turesson et al was restricted to the first decade of illness. All reported studies of systemic rheumatoid vasculitis have highlighted the fact that vasculitis usually occurs several years after the onset of arthritis. An analysis of 398 cases of systemic rheumatoid vasculitis reported in the literature through 1990 revealed a mean duration of RA of 11 years before vasculitis occurred (4). For example, in a hospital-based study of 32 patients with systemic rheumatoid vasculitis with peripheral neuropathy, the mean duration of RA was 16 years (range 2–47 years) (5). Had we restricted the study to only those cases observed within the first decade of RA, more than half (56%) of these complications would have been missed.

Before drawing any conclusion from the study conducted by Turesson et al, we would like to ask the authors to provide the incidence of rheumatoid vasculitis in their cohort of patients without limiting the analysis to the first decade of illness. With the complete data, which will increase the number of cases, especially in patients for whom the diagnosis had been made several decades ago, the incidence might no longer remain as stable as initially reported.

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1. Turesson C, McClelland RL, Christianson TJ, Matteson EL. No decrease over time in the incidence of vasculitis or other extraarticular manifestations in rheumatoid arthritis: results from a community-based study. Arthritis Rheum 2004;50:3729–31.
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Decrease over time in the incidence of systemic rheumatoid vasculitis: comment on the article by Turesson et al

To the Editor:

We read with interest the recent report by Turesson et al on the incidence of extraarticular manifestations of rheumatoid arthritis (RA) in Olmsted County, Minnesota (1). In contrast to our study in Norfolk, UK, which showed a decline in the incidence of systemic rheumatoid vasculitis over 15 years (2), those authors did not observe such a decline. There are several possible explanations for the different study results. The decrease in incidence of systemic rheumatoid vasculitis in our study only occurred after the mid-1990s (Figure 1), whereas their report does not include any data from after 1994. There were differences in case identification between the 2 studies because our study was hospital based whereas Turesson et al based their study in the community. However, it is likely that patients with severe extraarticular disease will present for

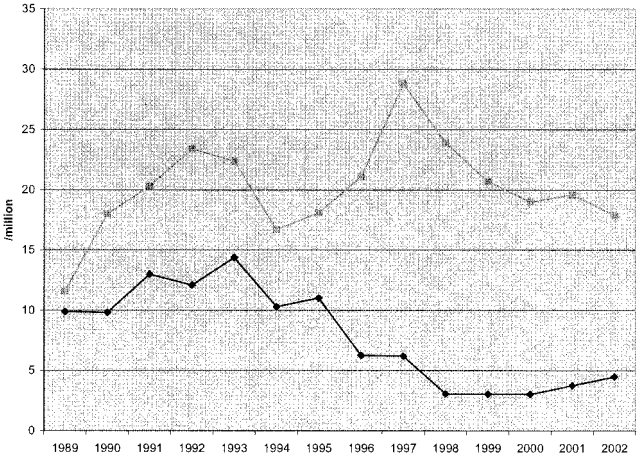

Figure 1. Incidence (cases per million population) of systemic rheumatoid vasculitis (♦) and primary systemic vasculitis (■). Each data point corresponds to the average incidence over a 3-year period, centered at the midpoint of the 3-year period.

hospital-based care at some stage as Turesson and colleagues acknowledge in their conclusion. Our study was based on the date of onset of vasculitis and not on presentation to the hospital or diagnosis of RA. Our methods were also likely to result in identification of a higher incidence of vasculitis compared with their study because we included all patients, regardless of the date of diagnosis or duration of followup. It is worth noting that over a 15-year period, we have not observed a change in the incidence of primary systemic vasculitis (Figure 1). This suggests that the decrease of systemic rheumatoid vasculitis observed in our study is a genuine reduction (3).

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1. Turesson C, McClelland RL, Christianson TJ, Matteson EL. No decrease over time in the incidence of vasculitis or other extraarticular manifestations in rheumatoid arthritis: results from a community-based study. Arthritis Rheum 2004;50:3729–31.
2. Watts RA, Mooney J, Lane SE, Scott DG. Rheumatoid vasculitis: becoming extinct? Rheumatology (Oxford) 2004;43:920–3.
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Reply

To the Editor:

We thank Dr. Puéchal and Drs. Watts, Lane, and Scott for their interest in our work and their comments. As pointed out by Dr. Puéchal, our results differ not only from those of the hospital-based study by Watts et al (1), but also from those of a study of rates of hospitalization due to RA-related complications in California (2), in which a decline over time in the rate of hospitalization due to vasculitis was observed. As discussed in our article, we believe that a thorough survey of a community-based sample provides a better estimate of the burden of severe extraarticular disease in patients with RA than data based on hospital registers. In addition, differences in case definitions may explain part of these discrepancies.

Dr. Puéchal suggests that our restricting the analysis to the first decade of illness might have affected the results, since a substantial number of patients present with vasculitis >10 years after disease onset. We agree that long-term followup would yield more information on possible changes over time. There is an inherent problem, however; there is no way we could have long-term data for patients with recently diagnosed RA. In order to avoid bias due to differences in length of followup, we have grouped the patients by decade of RA diagnosis and, for the purpose of the analysis, calculated cumulative incidence rates with truncated followup. As suggested by Dr. Puéchal, we have also analyzed the incidence of rheumatoid vasculitis beyond the first decade of illness. Since our survey was performed in 2001, long-term data for patients with RA diagnosed in 1985–1994 are not available. We analyzed the 20-year cumulative incidence of severe extraarticular disease by decade of diagnosis for patients with RA onset in 1955–1964, 1964–1975, and 1975–1984. The 20-year cumulative incidence rates for severe vasculitis were 3.6%, 4.3%, and 6.2%, respectively ($P = 0.88$). Thus, in our sample there is no evidence for a decline in the incidence of rheumatoid vasculitis, but we cannot exclude the possibility of a change in the 10-year cumulative incidence in patients diagnosed as having RA after 1994, nor can we exclude the possibility of a change in the incidence beyond the first decade of illness in patients diagnosed after 1984. Data on this can only be provided by future studies.

Drs. Watts, Lane, and Scott comment on some relevant differences between our study and theirs (1). However, their statement indicating that our report "does not include any data from after 1994" is not correct. Our followup was through December 31, 2000, although only patients with RA diagnosed up to 1995 were included. We did not see any decrease in the incidence of vasculitis in patients with onset of RA in 1985–1994 compared with patients with onset of RA before 1985, indicating that there was no major fall in the incidence of rheumatoid vasculitis in the 1990s corresponding to that observed by Watts et al (1).

We agree with Drs. Watts, Lane, and Scott that the differing patterns for the incidence of primary systemic vasculitis and systemic rheumatoid vasculitis observed in the Norfolk study are of major interest. However, we do believe that the best estimate of the incidence of extraarticular manifestations, including vasculitis, comes from thorough studies of defined populations of patients with RA.

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1. Watts RA, Mooney J, Lane SE, Scott DG. Rheumatoid vasculitis: becoming extinct? Rheumatology (Oxford) 2004;43:920–3.
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Hydroxychloroquine does not decrease serum methotrexate concentrations in children with juvenile idiopathic arthritis

To the Editor:

There is currently a consensus among physicians to treat juvenile idiopathic arthritis (JIA) aggressively, with methotrexate (MTX) as the gold standard (1). Combining MTX with hydroxychloroquine (HCQ) is common in patients with poor response to MTX alone. This combination has also been used to prevent the liver toxicity of MTX in rheumatoid arthritis (RA). However, the latter is only supported by 1 publication (2).

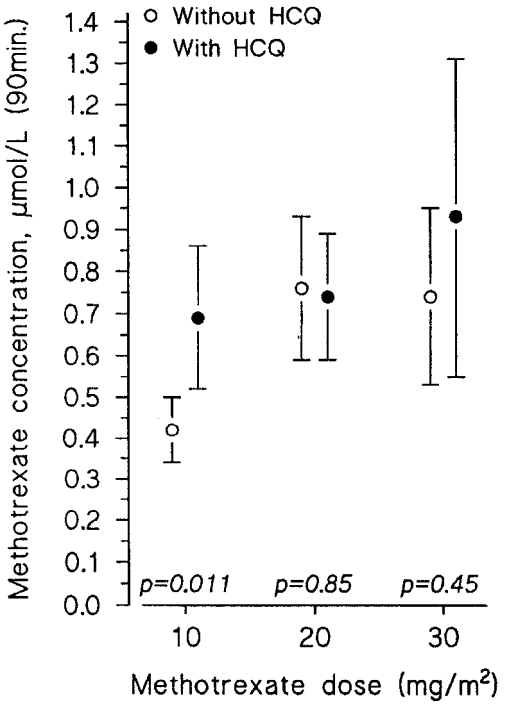

Figure 1. Serum methotrexate concentrations in patients with juvenile idiopathic arthritis (JIA) who were and those who were not receiving concomitant hydroxychloroquine (HCQ). *P* values were calculated by *t*-test with Hommel's modification of the Bonferroni procedure. Values are the mean with 95% confidence interval.

It has been reported that simultaneous administration of HCQ decreases the bioavailability of MTX in patients with RA (3). However, theoretically HCQ would increase the level of MTX through its inhibitory effect on aldehyde oxidase, which metabolizes MTX to 7-OH-MTX, the less active metabolite. We tested the effects of HCQ on MTX concentrations in children with JIA.

Of 105 consecutive JIA patients, 74 were included in this study and were divided into 3 groups according to their weekly MTX dosage (i.e., 10, 20, or 30 mg/m^2 [±10%] of body surface area). The numbers of patients receiving HCQ in the above dosage groups were as follows: 13 of 27, 17 of 36, and 4 of 11, respectively. The daily dosage of HCQ was ~5 mg/kg. The mean age of children receiving HCQ was higher than that of children receiving MTX alone, but the difference was not statistically significant. Sex distribution and use of nonsteroidal antiinflammatory drugs were similar in both groups.

MTX was administered before lunch (standard hospital food without any dairy products). Blood samples were obtained 90 minutes after intake of the drug. MTX concentrations were determined by fluorescence polarization immunoassay technology (TDX; Abbott, Abbott Park, IL). Interassay variations ranged from 5.1% to 7.3%.

When the concentrations were correlated with the MTX dose (Figure 1) it could be concluded that concomitant use of HCQ did not have any clear-cut effect on serum MTX concentrations in patients with JIA. Therefore, based on our results, the hypothesis that HCQ decreases the bioavailability of MTX does not seem to be valid. Interestingly, there are recent data showing that pharmacogenetic measures may help in monitoring MTX therapy (4,5). This should also be tested in patients taking the combination of MTX and HCQ.

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Does vitamin D supplementation contribute to the modulation of osteoarthritis by bisphosphonates? Comment on the article by Carbone et al

To the Editor:

We read with interest the article by Carbone et al on the relationship of antiresorptive drug use to structural findings in osteoarthritis (OA) in the Health, Aging and Body Composition Study (1). While the authors conclude that alendronate and estrogen decrease subchondral bone lesions as seen on magnetic resonance imaging (MRI), the effect of vitamin D supplementation in this population has not been discussed in their article.

In the study by Carbone et al, statistically significant calcium supplementation use was observed in antiresorptive drug users compared with antiresorptive drug nonusers. It is reasonable to suspect that the calcium supplementation may have been given with vitamin D supplementation; the recommended dosage of vitamin D is 400–800 IU/day (2). It has already been established that hypovitaminosis D is associated with progression of OA. Conversely, vitamin D supplementation may be beneficial. In a study of hip OA, a low serum level of 25-hydroxyvitamin D was associated with incident joint space narrowing; the group with incident hip OA had lower reported levels of vitamin D than those subjects who did not have incident hip OA (3). In the Framingham Osteoarthritis Study, decreased dietary intake of vitamin D has been associ-

ated with progression of knee OA; low serum levels of vitamin D and low dietary intake appear to predict osteophyte growth and cartilage loss (4).

In the Health, Aging and Body Composition Study, the cohort receiving antiresorptive therapy may be receiving better vitamin D supplementation, and this may be contributing to the decrease in subchondral lesions seen on MRI. In the same way, higher levels of vitamin D are associated with less severe radiographic changes in OA of the knee and hip. Although the radiographic effect was not observed in the Health, Aging and Body Composition Study, the discrepancy may reflect a difference in radiographic technique (5); investigators in the Framingham Study used a standard anteroposterior knee radiograph (6), while those in the Health, Aging and Body Composition Study used a fixed-flexion technique. Since investigators in the Health, Aging and Body Composition Study recorded over-the-counter drugs and supplements used in the 2 weeks prior to the study visit, Carbone et al may still be able to report this information, which would add to our knowledge of interventions that are useful for the management of OA.

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Reply

To the Editor:

We thank Drs. DeMarco and Constantinescu for their comments. In accordance with their suggestions, we reanalyzed our data taking into account concurrent use of vitamin D supplements.

We defined use of vitamin D supplements as use of any vitamin D supplements. By this definition, 16.1% of our subjects were using vitamin D supplements. Overall, we found no significant association between the use of vitamin D supplementation and radiographic changes of knee OA, MRI parameters of knee OA (including bone attrition, osteophytes, bone marrow abnormalities, or cartilage lesions), or scores on the Western Ontario and McMaster Universities Osteoarthritis Index ($P > 0.13$ for all parameters). We also adjusted for use of vitamin D supplementation in all of our analyses examining the association of antiresorptive medication use with structural changes and symptoms of knee OA. Our results were essentially unchanged by this additional adjustment.

Levels of 25-hydroxyvitamin D were not measured at this time point in our cohort, so we were not able to assess whether adjustment for actual levels of 25-hydroxyvitamin D might have influenced our results. Although we were not able to find a direct association between use of vitamin D supplementation and OA of the knee in this cross-sectional study, we agree that the relationship of vitamin D to OA of the knee does merit further study.

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Anti-SSA/Ro–related congenital heart block in two family members of different generations: comment on the article by Clancy et al

To the Editor:

The recent report by Clancy et al on HLA class II and tumor necrosis factor α associations in neonatal lupus (1) confirms that the HLA portion of the extended haplotype DQB1*02;DRB1*03 provides the genetic predisposition for generation of anti-Ro/La antibodies that cross the placenta and bind apoptotic neonatal keratinocytes and fetal cardiocytes, thus initiating an inflammatory response. Those authors thus suggest that the risk for induction of neonatal lupus may be genetically transmitted. Congenital heart block (CHB), the main feature of neonatal lupus, has been found in 1 or more offspring of the same mother (in siblings or twins) (2,3), but it has not been described to occur in family members of different generations, even if dated cardiology records confirm its existence (4). We recently observed a family in which both the mother and the daughter had anti-SSA/Ro antibodies and transmitted CHB to their respective infants, as described below.

A 26-year-old woman was referred to us in August 2001, during the eighth week of her first pregnancy. Sjögren's syndrome had been diagnosed 1 year earlier on the basis of dry mouth, dry eyes, anti-SSA/Ro antibodies (52 and 60 kd), and a first-degree lymphocytic infiltration in a minor salivary gland.

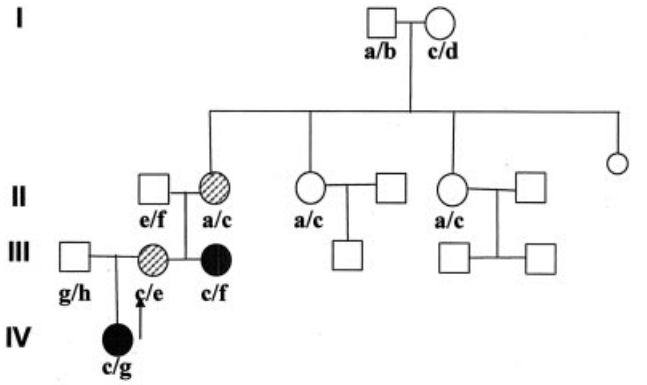
The family history revealed CHB in her only sister. A normal heart rate and anatomy were recorded during the first fetal echocardiography performed at week 17 of gestation. At week 18 of gestation the patient exhibited swelling and erythema of her toes, particularly when standing. She did not report having pain or other symptoms, and results of arterial and venous Doppler ultrasonography were normal. Fetal ultrasonography at week 19 revealed a normal heart rate.

Sonography performed at week 22 revealed bradycardia in the fetus, which was confirmed by the finding of an advanced second-degree atrioventricular (AV) block on fetal echocardiography. At that time the original treatment plan of methylprednisolone (4 mg/day) was replaced by dexamethasone (4 mg/day) and weekly plasmapheresis: in the presence of an incomplete AV block, we used this therapy to avoid progression to a complete one. This regimen was maintained until delivery. The swelling and erythema of the patient's toes disappeared shortly after plasmapheresis was begun. Two weeks later, at week 24, fetal echocardiography showed episodes of sinus heart rate to 115–130 beats/minute along with a predominant second-degree AV block. Serial echocardiography, subsequently performed every 2 weeks, confirmed this finding. Cardiac anatomy and function in the fetus were normal, and no pericardial or pleural effusions or ascites were detected.

At week 39, a 2,440-gm girl was delivered by planned, uncomplicated cesarean section. Apgar scores were 9 after 1 minute and 10 after 5 minutes. The infant appeared healthy at birth, and no signs of cutaneous lesions were noted. Results of all standard blood tests, including IgG, IgA, and IgM levels, were normal. A 24-hour electrocardiogram (EKG) recording showed a predominant 2:1 Mobitz II second-degree AV block, with a mean heart rate of 75 beats/minute along with episodes of sinus heart rate >100 beats/minute. At 14 months of age the child developed an advanced second-degree block, which at 27 months of age progressed to a complete third-degree AV block with a mean heart rate of 72 beats/minute (ranging from 48 to 103 beats/minute), not requiring pacemaker implantation. The infant had anti-SSA/Ro antibodies (52 and 60 kd) at birth but became seronegative by 8 months of age. The levels of SSA/Ro antibodies in the mother were unaltered during pregnancy as measured by enzyme-linked immunosorbent assay (ELISA) in 6 consecutive serum samples.

Nine family members of the patient were available for study (Figure 1). The subjects, all white, were personally interviewed and clinically examined. Signs or symptoms of autoimmune diseases were sought, EKG was performed, and blood samples for HLA typing and autoantibody testing were obtained. In particular, serum IgG anti-SSA/Ro and anti-SSB/La antibodies were evaluated using an in-house counterimmunoelectrophoresis kit and by ELISA using plates coated with recombinant human 52- and 60-kd SSA/Ro and SSB/La proteins, respectively (Diamedix Delta Biologicals, Pomezia Croma, Italy).

Family pedigree and HLA haplotypes are outlined in Figure 1, in which the 2 anti-SSA/Ro–positive women (the index patient and her mother) and their daughters with CHB are indicated. Relevant findings were present in the index patient's mother. She was a 51-year-old woman with evident clinical and serologic features of a connective tissue disease, including fatigue, dry mouth, dry eyes, photosensitivity, diffuse arthralgias, oral ulcers, leukopenia with lymphocytopenia, and



a	A*23	B*50	DRB1*03	DRB3*	DQB1*02
b	A*32	B*07	DRB1*10	-	DQB1*05
c	A*01	B*08	DRB1*03	DRB3*	DQB1*02
d	A*68	B*35	DRB1*11	DRB3*	DQB1*03
e	A*68	B*27	DRB1*16	DRB5*	DQB1*05
f	A*03	B*51	DRB1*11	DRB3*	DQB1*03
g	A*24	B*51	DRB1*11	DRB3*	DQB1*03
h	-	B*44	-	-	-

Figure 1. Pedigree of family members and HLA haplotypes. Solid circles = congenital heart block; hatched circles = anti-Ro/SSA antibodies. Arrow indicates the index patient.

marked blanching of the fingers upon exposure to cold. Her antibody pattern was characterized by anti-SSA/Ro + antibodies (52 and 60 kd), antinucleolar antibodies at high titer as determined by immunofluorescence on HEp 2000 cells, and type 2 antimitochondrial antibodies as determined by immunoblotting. The first of her 2 pregnancies was normal and she gave birth to a healthy female infant (the index patient). Fetal bradycardia was detected during week 20 of her second pregnancy (May 1981). This went untreated, and at week 40 a bradycardic female infant with neonatal asphyxia was delivered. The first EKG performed on the infant, at 8 months of age, revealed a complete third-degree AV block. The worsening of the bradycardia made implantation of a pacemaker necessary when the subject reached the age of 17 years. She currently has incomplete Raynaud's phenomenon, characterized by blanching of fingers upon cold exposure. She is nonetheless negative for all examined antibodies including antinuclear, anti–extractable nuclear antigen, anti–native DNA, anticentromere, lupus anticoagulant, anticardiolipin, and antimitochondrial antibodies.

Several findings in this family study were intriguing. First, the finding of 2 women in the same family but from different generations (mother and daughter) who each had anti–52-kd SSA/Ro antibodies and delivered a female infant with CHB leads us to hypothesize that the risk for induction of anti-SSA/Ro–related CHB may be genetically transmitted.

Second, the HLA haplotype A*01;B*08;DRB1*03;DRB3*;DQB1*02 (haplotype c in Figure 1) was exhibited by all of the women in this family group and included several alleles previously reported to occur at high frequency in mothers of children with CHB (5,6). Moreover some of these alleles (B*08, DRB1*03, and DQB1*02) are generally associated with anti–52-kd SSA/Ro antibodies (6), a reasonable

marker for risk of CHB transmission (7). However, only the index patient and her mother had anti–52-kd SSA/Ro antibodies and delivered infants with CHB (Figure 1). It is interesting that the index patient's mother and 2 maternal aunts carried the same maternal and paternal haplotypes (a/c) with class II alleles in homozygous combination (Figure 1). But only the index patient's mother had anti–52-kd SSA/Ro antibodies and gave birth to a child with CHB, while her 2 sisters had no antibodies and delivered, respectively, 1 and 2 healthy infants.

It has been hypothesized that a rare allelic variant primarily associated with risk for CHB and/or with an enhanced potential for synthesizing pathogenic anti-Ro/La antibodies could occur in genetically predisposed women (5). This undefined variant was perhaps present in the mother of our index patient, who exhibited the haplotype that is reported to occur frequently in mothers of children with CHB. Furthermore, the presence of pathogenic anti–52-kd SSA/Ro antibodies also in 1 of her daughters would indicate that this variant may be genetically transmitted as a nondominant character. It is also interesting to observe that the index patient's daughter and sister, who were both affected with CHB, had the same maternal haplotype (c), while the paternal haplotypes (f and g) differed only with respect to 1 allele. The significance of this immunogenetic similarity is difficult to interpret, since some previous reports have described discordance for CHB in monozygotic twins (2,3). No significant conclusions can be drawn from our data concerning a single family. Extending these studies on anti-SSA/Ro–related CHB to earlier generations of these families could verify our findings. However, because this antibody-transmitted disorder has only recently been defined (8,9) and the methods used to study fetal heart rate abnormalities in the past were unreliable, this would be a difficult feat.

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Reply

To the Editor:

We thank Dr. Ruffatti and colleagues for their interest in our work. They report on a family in which CHB is present in 2 generations. Two points are notable, one related to maternal and fetal genetics and the risk of CHB, and the other to the progression of AV nodal dysfunction subsequent to the clearance of maternal autoantibodies.

The family they describe illustrates that the risk of CHB comprises both maternal and fetal components. The mother contributes a "necessary" factor, i.e., anti-SSA/Ro antibodies, the synthesis of which is linked to her own HLA–DRB1*03 (Harley JB, Alexander EL, Bias WB, Fox OF, Provost TT, Reichlin M, et al. Anti–Ro (SS-A) and anti–La (SS-B) in patients with Sjögren's syndrome. Arthritis Rheum 1986;29:196–206). The fetal contribution is less clear, but does not appear to rely solely on HLA–DRB1*03. HLA class II molecules were analyzed across 3 generations, and there was inheritance of DRB1*03 in 6 of 6 mother/child pairs. However, 2 of the 6 children did not develop autoantibodies or incur CHB, suggesting that the role of HLA in immunologic events related to CHB is difficult to assign. In contrast, in our study the majority of children with neonatal lupus rash had the -308A promoter allele of tumor necrosis factor α (TNFα). This allele was associated with the presence of both HLA–DQB1*02 and HLA–DRB1*03 in children with rash significantly more often than in anti-SSA/Ro–exposed children without rash (both with CHB and unaffected). Clinically, the cutaneous manifestation resembles subacute cutaneous lupus erythematosus (SCLE). Neonatal lupus rash and SCLE share the extended DQB1*02;DRB1*03 haplotype, which, in the case of neonatal lupus rash, contributes a "double hit": the maternal component is the predisposition to autoantibody, and the child's component is the TNFα portion (-308A) of 6p.

The deterioration of block to third degree at 27 months

was also noted in several children enrolled in the US Research Registry for Neonatal Lupus (Askanase AD, Friedman DM, Dische MR, Dubin A, Starc T, Katholi MC, et al. Spectrum and progression of conduction abnormalities in infants born to mothers with anti-SSA/Ro-SSB/La antibodies. Lupus 2002;11: 145–51). These cases suggest that events initiated in utero (despite transient clinical benefit with dexamethasone) can progress to further scarring. Understanding the fetal/neonatal contribution to this unleashed fibrotic process may lead to novel therapeutic approaches.

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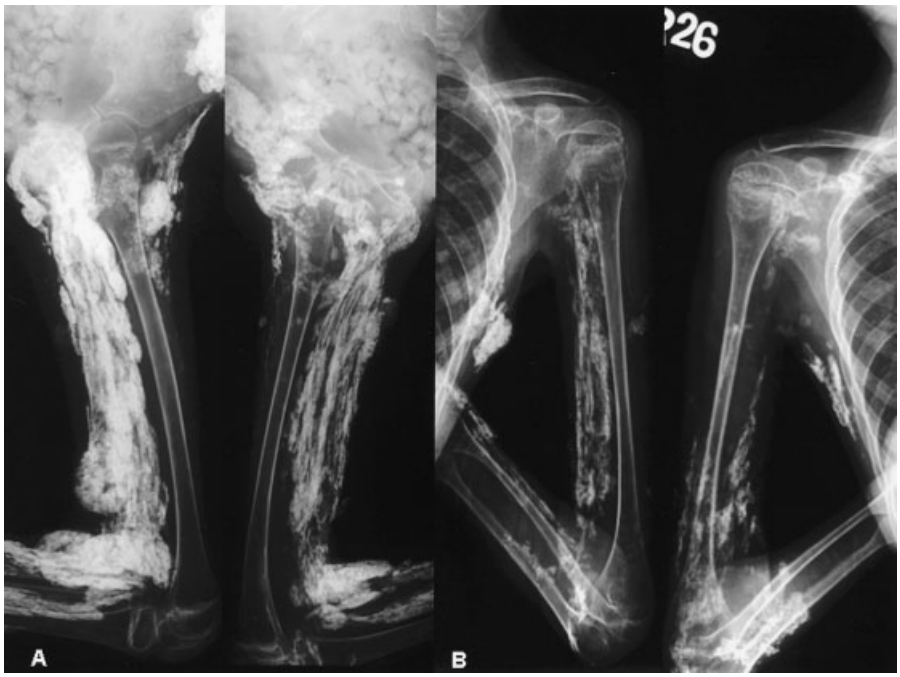
Clinical Images: Calcinosis universalis complicating juvenile dermatomyositis



The patient, a 9-year-old girl, was referred to the department of pediatric rheumatology for evaluation of diffuse soft tissue calcification. She had been diagnosed as having juvenile dermatomyositis (DM) at the age of 7 years, when progressive limb weakness and erythema of the eyelids (heliotrope patch) were noted. Radiographic studies revealed severe diffuse osteoporosis, extensive deep muscular calcareous deposits in all 4 extremities, and some scattered calcific spots in the trunk (**A** and **B**), compatible with calcinosis universalis. The calcific nodules gradually increased in size, ulcerated, and restricted her joint mobility. Laboratory studies revealed hypercalcemia, a low serum level of intact parathyroid hormone, and high urinary excretion of bone resorption markers. Therapy with probenecid, aluminum hydroxide, and diltiazem was administered for 6 months without improvement. Bisphosphonate was added to the treatment regimen because of the high bone turnover; the efficacy of this treatment is not yet known. Calcinosis occurs more commonly in juvenile DM than in adult DM. The extreme form, calcinosis universalis, is a rare but disabling complication (1). Calcification may be metabolic or dystrophic, and in our patient was determined to be metabolic based on the increased calcium turnover (2). Due to the lack of knowledge of its mechanisms, no successful treatment of calcinosis universalis has been identified to date. Inconsistent success has been reported with probenecid, aluminum hydroxide, warfarin, and diltiazem (2). Further investigation of disease mechanisms is needed so more effective therapeutic strategies may be developed.

1. Bowyer SL, Blane CE, Sullivan DB, Cassidy JT. Childhood dermatomyositis: factors predicting functional outcome and development of dystrophic calcification. J Pediatr 1983;103:882–8.
2. Mukamel M, Horev G, Mimouni M. New insight into calcinosis of juvenile dermatomyositis: a study of composition and treatment. J Pediatr 2001;138:763–6.

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